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HEALTH TECHNOLOGY BRIEFING AUGUST 2020

Osimertinib for EGFR-positive non-small cell lung cancer - adjuvant

NIHRIO ID	26787	**NICE ID**	10481
Developer/Company	AstraZeneca UK Ltd.	**UKPS ID**	658113

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Osimertinib is in clinical development as an adjuvant treatment for resectable, early stage non-small cell lung cancer (NSCLC). Lung cancer is one of the most common and serious types of cancer and NSCLC is the most common type of lung cancer. An adjuvant treatment is an additional cancer treatment given after the primary treatment, to lower the risk of the cancer returning. Resectable cancer means that the cancer can be removed by surgery, which means the cancer is normally in earlier stages. A proportion of patients have mutations to the protein epidermal growth factor receptor (EGFR) which controls cell growth. There are currently no recommended EGFR-targeted therapies for early stage NSCLC.

Osimertinib is an inhibitor of EGFR, which binds specifically to mutant forms of EGFR to inhibit growth of tumour cells. Osimertinib is administered as an oral tablet and has demonstrated both safety and effectiveness in a phase III clinical trial. Osimertinib is already approved for advanced NSCLC and if licensed for the early stage disease, it will offer an additional treatment option for patients with EGFR-positive NSCLC, after complete tumour resection.

PROPOSED INDICATION

Treatment of patients with epidermal growth factor receptor mutation (EGFR)m positive stage IB-IIIA non-small cell lung carcinoma (NSCLC), following complete tumour resection.[1]

TECHNOLOGY

DESCRIPTION

Osimertinib (Tagrisso, AZD9291) is an orally available, irreversible, third-generation, mutant-selective EGFR inhibitor, with potential antineoplastic activity. Osimertinib is a Tyrosine Kinase Inhibitor (TKI). It is an irreversible inhibitor of EGFRs harbouring sensitising-mutations (EGFRm) and TKI-resistance mutation T790M.[2] Upon oral administration, osimertinib selectively and covalently binds to and inhibits the activity of the mutant forms of EGFR, thereby preventing EGFR-mediated signalling. This may both induce cell death and inhibit tumour growth in EGFR-overexpressing tumour cells. EGFR, a receptor tyrosine kinase overexpressed or mutated in many types of cancers, plays a key role in tumour cell proliferation and tumour vascularization. As this agent is selective towards mutant forms of EGFR, its toxicity profile may be reduced as compared to non-selective EGFR inhibitors, which also inhibit wild-type EGFR.[3]

Osimertinib is in clinical development for the treatment of stage Ib - IIIa EGFR mutation positive NSCLC after complete tumour resection. In the phase III trial, ADAURA (NCT02511106), osimertinib was administered at either 80 mg or 40 mg orally, once daily.[1,4]

INNOVATION AND/OR ADVANTAGES

Research has identified genetic drivers of NSCLC, including mutations to the EGFR gene, which occur in 10%–35% of patients with NSCLC.[5] There are currently no NICE recommended EGFR targeted therapies for the adjuvant treatment of early stage EGFR positive NSCLC.[6,7]

Osimertinib is a novel EGFR tyrosine kinase inhibitor (TKI), the structure and pharmacology of which are distinct from other third-generation EGFR TKIs. It shows 200-fold selectivity for T790M/L858R protein over wild-type EGFR.[5]

In the phase III clinical trial, ADAURA (NCT02511106), adjuvant treatment with osimertinib (Tagrisso) demonstrated an 83% reduction in the risk of disease recurrence or death in patients with stage II to IIIA EGFR-mutant NSCLC.[8] In addition, based on the efficacy findings in ADAURA, the study will be unblinded early under the recommendation from an Independent Data Monitoring Committee. Osimertinib did not lead to any additional safety concerns in the randomized, double-blinded clinical trial.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Osimertinib is currently licensed in the EU/UK as a monotherapy for:[2]

- The first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations
- Treatment of adult patients with locally advanced or metastatic EGFR T790M mutation positive NSCLC

Common or very common side effects of osimertinib include: diarrhoea; eyelid pruritus; increased risk of infection; nail discolouration; nail disorders; respiratory disorders; skin reactions; stomatitis.[9]

In July 2020, osimertinib was granted breakthrough therapy designation (BTD) by the US Food and Drug Administration (FDA) for the adjuvant treatment of patients with early-stage (IB, II and IIIA) EGFR NSCLC after complete tumour resection with curative intent. The FDA granted BTD based on the data from the phase III ADAURA trial, which demonstrated a statistically significant and clinically meaningful improvement in disease-free survival (DFS) in the adjuvant treatment of stage IB-IIIA EGFRm NSCLC patients, reducing the risk of disease recurrence or death by 79%.[10]

Osimertinib is currently in phase II/III clinical development for the treatment of NSCLC.[11]

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is one of the most common and serious types of cancer. There are usually no signs or symptoms in the early stages of lung cancer, but many people with the condition eventually develop symptoms such as a persistent cough, coughing up blood, persistent breathlessness, unexplained tiredness and weight loss, and/or an ache or pain when breathing or coughing.[12]

Smoking cigarettes is the single biggest risk factor for lung cancer and is responsible for more than 70% of cases. Other risk factors include passive smoking, radon (a radioactive gas), and exposure to chemicals such as arsenic, asbestos, beryllium, cadmium, coal/coke, silica and nickel.[13]

NSCLC accounts for around 85-90% of lung cancers in the UK.[14] There are three main types of NSCLC:[15]

- Adenocarcinoma – starts in the mucus making gland cells in the lining of airways
- Squamous cell cancer – develops in the flat cells that cover the surface of the airways
- Large cell carcinoma – the cancer appears large and round under the microscope

In addition to being diagnosed by type of lung cancer, patients will also have the cancer graded. Grading is based on how cells look under a microscope, and gives an estimate of how quickly or slowly the cancer is growing, and whether it is likely to spread.[16] Stage Ib, and II are in the early stages of cancer; stage III cancer is locally advanced cancer. In the early stages, cancer can be resectable, meaning the cancer can be removed by surgery.[17,18] Possible treatments for stage III cancer include: chemoradiotherapy followed by surgery; surgery followed by chemotherapy; immunotherapy following chemoradiotherapy; targeted therapies.[19]

"Sensitising mutations" in EGFR (EGFRm+) refer to exon 19 deletions and exon 21 L858R point mutations.[5] The latter results in arginine replacing leucine at codon 858 (L858R). These mutations can result in constitutive activation of signal transduction pathways, leading to cell proliferation or anti-apoptosis, regardless of the presence of extracellular ligand.[20]

CLINICAL NEED AND BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2017. There are around 48,000 new lung cancer cases in the UK yearly. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 years (2015-2017). Incidence rates

for lung cancer are projected to fall by 7% in the UK between 2014 and 2035, to 88 cases per 100,000 people by 2035.[21]

In 2018/19 there were 107,010 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 128,985 finished consultant episodes (FCEs), resulting in 249,196 FCE bed days.[22]

According to the National Cancer Registration and Analysis Service (NCRAS), there were 18,175 diagnosed cases of stage I-III lung cancer in 2017.[23] In the UK is estimated that up to 85% of lung cancer cases are NSCLC, applying this figure to the number of stage III lung cancer cases diagnosed in 2017, it can be estimated that approximately 15,448 cases diagnosed with stage I-III in 2017 were NSCLC.[15]

In England between 2013 and 2017, the age-standardised net lung cancer survival for stage I was 87.7% at one year and 56.6% at five years; for stage II, 73.0% at one year and 34.1% at five years; for stage III, 48.7% at one year and 12.6% at five years.[24] There are around 35,300 lung cancer deaths in the UK every year (based on data from 2015-2017). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.[21] In England and Wales in 2018 there were 29,604 deaths with malignant neoplasm of bronchus and lung (ICD-10 codes C34) recorded as the underlying cause.[25]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer and the general health of the patient. All patients are advised to stop smoking as soon as diagnosis is suspected; nicotine replacement therapy and other therapies may be offered.[26] The main treatment options for stage I, II and III NSCLC are surgery, chemotherapy and radiotherapy.[18]

For people who are well enough and for whom curative intent is suitable, surgery (bronchoangioplastic surgery, bilobectomy or pneumonectomy) may be offered. For people with stage I–IIA NSCLC who decline lobectomy or in whom it is contraindicated, radical radiotherapy with stereotactic ablative radiotherapy (SABR) or sublobar resection is offered. Patients undergoing surgery will also be offered chemotherapy. [26]

CURRENT TREATMENT OPTIONS

Patients with NSCLC are offered the following chemotherapy drugs, in combination with cisplatin or carboplatin:[27]

- Vinorelbine
- Gemcitabine
- Paclitaxel (Taxol)
- Docetaxel (Taxotere)
- Etoposide
- Pemetrexed

PLACE OF TECHNOLOGY

If licensed, osimertinib will offer an additional treatment option for patients with EGFRm positive stage IB-IIIA NSCLC, following complete tumour resection.[1]

CLINICAL TRIAL INFORMATION

Trial	**ADAURA,** NCT02511106**,** A Phase III, Double-blind, Randomized, Placebo-controlled Multi-centre, Study to Assess the Efficacy and Safety of AZD9291 Versus Placebo, in Patients With Epidermal Growth Factor Receptor Mutation Positive Stage IB-IIIA Non-small Cell Lung Carcinoma, Following Complete Tumour Resection With or Without Adjuvant Chemotherapy. **Phase III** – active, not recruiting **Location(s):** Europe (excluding the UK), US and other countries **Primary completion date:** January 2020
Trial design	Randomised, parallel assignment, triple-blinded
Population	- N = 688 - EGFR mutation positive stage IB-IIIA NSCLC, following complete tumour resection with or without adjuvant chemotherapy - Adults aged 18 to 130 years old
Intervention(s)	Osimertinib (80 mg or 40 mg orally, once daily), in accordance with the randomization schedule.
Comparator(s)	Matched placebo
Outcome(s)	Disease free survival (DFS) [Time frame: from date of randomization until date of disease recurrence or death (by any cause in the absence of recurrence). Estimated median time to event of 46 and 66 months for those on placebo and osimertinib, respectively.] For full list of outcomes, see trial record
Results (efficacy)	In the primary endpoint of DFS in patients with Stage II and IIIA disease, adjuvant treatment (after surgery) with Tagrisso reduced the risk of disease recurrence or death by 83% (based on a hazard ratio [HR] of 0.17; 95% confidence interval [CI] 0.12, 0.23; p<0.0001). DFS results in the overall trial population, Stage IB through IIIA, a key secondary endpoint, demonstrated a reduction in the risk of disease recurrence or death of 79% (based on a HR of 0.21; 95% CI 0.16, 0.28; p<0.0001).[28] At two years, 89% of patients in the trial treated with Tagrisso remained alive and disease free versus 53% on placebo. Consistent DFS results were seen across all subgroups, including patients who were treated with surgery followed by chemotherapy and those who received surgery only, as well as in Asian and non-Asian patients.[28]
Results (safety)	Osimertinib was well tolerated with a safety profile consistent with its known safety profile (diarrhoea, paronychia, dry skin, and pruritis being the most common). There were no adverse events leading to death in the osimertinib arm. The rate of grade 3-4 adverse events was low. Interstitial lung disease was reported in 10 (3%) patients in the osimertinib arm and in 0 patients in the placebo group; cardiac QTc prolongation was

	reported in 22 patients (7%) in the osimertinib arm and 4 patients (1%) in the placebo arm.[29]

ESTIMATED COST

Osimertinib is already marketed in the UK for the treatment of locally advanced or metastatic NSCLC with activating EGFR mutations or EGFR T790M mutations[2]; a pack of 30 x 40mg tablets costs £5770.00; a pack of 30 x 80mg tablets costs £5770.00.[9]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). March 2019.
- NICE technology appraisal guidance. Pemetrexed for the treatment of non-small cell lung cancer (TA124). August 2007.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[30]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[31]

ADDITIONAL INFORMATION

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